11C

P.O. Box 747
Falls Church, Virginia 22040-0747
Phone: (703) 205-8000
Fax: (703) 205-8050
(703) 698-8590 (GIV)

Birch, Stewart, Kolasch & Birch, LLP

Fax

To:	Examiner Covington	**From:**	David R. Murphy (Reg #22.751)
Fax:	703 746 5318	**Date:**	12 June 2003
Phone:		**Pages:**	(including cover sheet) 12
Your Ref.:	App #09/846,259	**Our Ref.:**	0425-0819P
Re:	Our 10 June 2003 Conference	**CC:**	

☒ **Urgent** ☒ **For Review** ☒ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

Comments:

Thank you very much for telephoning our offices on 10 June 2003. It is our understanding, based on that conference, that if the application were amended as shown on the attached sheets that all outstanding issues would be resolved and that you would pass the case to issue. No prior art was discussed.

If our understanding is correct please so inform us by any means convenient to you. We reliably receive e-mail sent to mailroom@bskb.com.

As soon as we have your response we will contact our client, who will determine whether, and in what manner the application will be amended.

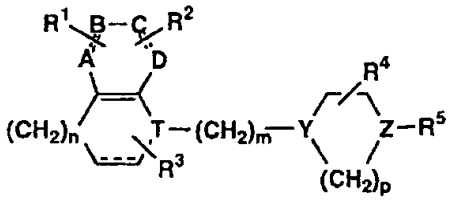
David R. Murphy

App # 09/846,259
Dkt # 0425-0189P

What is claimed is:

(currently amended)

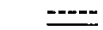
1. A ~~1,4-substituted cyclic amine derivative represented by the following~~ compound of formula (I):



(I)

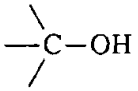
wherein A, B, C, D, and T are the same or different from one another and each represents methine or nitrogen, provided that one and only one of them represents nitrogen;

the bond represented by the following formula:

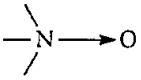


represents a single or double bond;

Y and Z are the same or different from each other and each represents methine, nitrogen, a group represented by the following formula:



or a group represented by the following formula:



provided at least one of them represents nitrogen;

R^1 and R^2 are the same or different from each other and each represents

6-12-03

hydrogen, halogeno, hydroxy, lower alkylsulfonylaminoalkyl, lower halogenated-alkylsulfonylaminoalkyl, 2-pyrrolidinon-1-yl, 1-hydroxy-1-(methoxypyridyl)methyl, methoxypyridylcarbonyl, 1,3-propanesultum-2-yl, lower hydroxypiperidyl-carbonylalkyl, lower hydroxyalkylamidoalkyl, lower halogenated-alkylamidoalkyl, lower dihalogenatedalkylamidoalkyl, ~~lower heteroarylamidoalkyl~~, lower hydroxyalkylamidoalkyl, optionally substituted amino, nitro, lower alkyl, lower alkoxy, lower acyl, lower alkoxyalkoxy, cyano, lower alkylsulfonyl, sulfonylamido, hydroxy-lower alkyl, hydroxy-lower alkoxy, lower alkoxycarbonylamino, lower alkylsulfonylamino, N-lower alkylalkylsulfonylamino, lower acylamino, optionally substituted aminoalkyl, optionally N-substituted lower acylaminoalkyl, optionally substituted aryl, optionally substituted arylsulfonylamino, lower alkylsulfonyloxy, hydroxyiminomethyl, (2-pyrrolidon1-yl)methyl, (2-piperidon-1-yl)methyl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heteroarylalkyl, cycloalkylcarbonylaminoalkyl, optionally substituted ureido, optionally substituted ureido-lower alkyl, succinimido, (succinimido-1-yl)-lower alkyl, amido, optionally substituted carbamoyl, optionally substituted carbamoyl-lower alkyl, optionally substituted thiocarbamoyllower alkyl, formyl, aromatic acyl, heteroarylcarbonyl, halogenated lower alkyl, (2-imidazolidinon -1-yl)methyl, (2,4-imidazolidinedion-3-yl)methyl, (2-oxazolidon3-yl)methyl, (glutarimido-1-yl)methyl, optionally substituted heteroarylhydroxyalkyl, cyano-lower alkyl, 1-hydroxy lower cycloalkyl, (2,4-thiazolidinedion-3-yl)methyl, optionally substituted 4-piperidylmethyl, heteroarylacyl, pyrrolidinylcarbonyl-lower alkyl, optionally substituted aminosulfonylalkyl, carboxy-lower alkyl, or lower alkylamidoalkyl; or alternatively R^1 and R^2 together may form optionally substituted alicycle, optionally substituted heterocycle or alkylenedioxy, provided

OM 6-12-03

these rings may be substituted;

R^3 represents hydrogen, halogeno, lower alkyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, formyl, optionally substituted aralkyloxy, hydroxy-lower alkoxy, optionally substituted sulfamoyl, or optionally N-substituted sulfamoyl-lower alkyl;

R^4 represents hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxyalkyl, optionally aryl-substituted aryloxyalkyl, or optionally aryl-substituted aralkyloxyalkyl;

R^5 represents lower alkyl, lower acyl, lower alkoxycarbonyl, aromatic acyl, or a group represented by the following formula:

$$-Q^1-(CH_2)_S-Q^2-R^6$$

wherein Q^1 and Q^2 are both single bonds, or one of them is a single bond while the other represents oxygen, carbonyl, a group represented by -NHCO-, a group represented by $-NHSO_2-$, or a group represented by $>CH-R^7$, wherein R^7 represents hydroxy, lower alkyl or halogeno:

s represents 0 or an integer of 1 to 6; and

R^6 represents optionally substituted aryl, (optionally substituted heteroaryl,) (optionally substituted benzoheteroaryl) 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzothiazolyl, or cyano;

n represents 1;

m represents 0 or an integer of 1 to 6; and

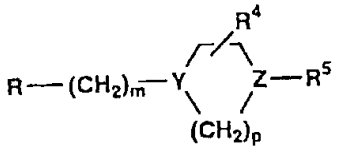
p represents an integer of 1 to 3,

or 4
~~and~~ pharmacologically acceptable salts thereof.

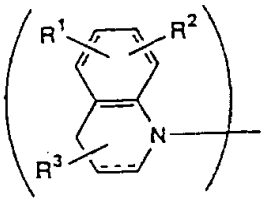
6-12-03

(currently amended)

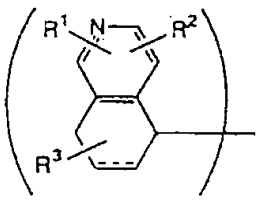
2. A ~~1,4-substituted cyclic amine derivative represented by the following~~ compound of formula:



wherein R represents a substituent of the formula:



or



wherein the bond represented by the following formula:

and R^1, R^2, R^3, R^4, R^5, Y, Z, m, and p are each as defined in claim 1, ~~and~~ or a pharmacologically acceptable salts thereof.

(currently amended)

3. The ~~1,4-substituted cyclic amine derivative as set forth in~~ compound of claim 1 or a pharmacologically acceptable salt thereof, wherein m is 0 and p is 2.

(currently amended)

4. The ~~1,4-substituted cyclic amine derivative as set forth in~~ compound of claim 1 or a pharmacologically acceptable salt thereof, wherein Y is methine and Z is nitrogen.

6-12-03

(currently amended)

5. The ~~1,4-substituted cyclic amine derivative as set forth in~~ compound of claim 1 or a pharmacologically acceptable salt thereof, which is a compound selected from among the following ones:

(267)

1-{1-[2-(4-methoxyphenyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(268) 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(269) 1-[1-(4-cyanopropyl)piperidin-4-yl]-7-methoxy-1,2,3,4-tetrahydroquinoline,

(270)

1-{1-[2-(2-thienyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(271)

1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7,8-dimethoxy-1,2,3,4-tetrahydroquinoline,

(272) 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7,8-methylenedioxy-1,2,3,4-tetrahydroquinoline,

(273) 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7-methoxy-8-methyl-1,2,3,4-tetrahydroquinoline,

(274) 1-{1-[2-(4-fluorophenyl)-2-oxoethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(275) 1-{1-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(276) 1-{1-[2-(4-fluorophenyl)-2-fluoroethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline, and

(283) 5-{4-[2-(4-fluorophenyl)ethyl]piperazin-1-yl}-5,6,7,8-tetrahydroisoquinoline.

6-12-03

(currently amended)

6. A pharmaceutical composition comprising a therapeutically effective amount of the ~~1,4-substituted cyclic amine derivative or salt as set forth in~~ compound of claim 1 or its salt in combination with a pharmaceutically acceptable carrier.

(currently amended) and

7. An agent for treating, ameliorating, ~~and preventing~~ diseases against which serotonin antagonism is efficacious, which ~~contain~~ contains as the active ingredient the ~~1,4-substituted cyclic amine derivative as set forth in~~ compound of claim 1 or a pharmacologically acceptable salt thereof.

a compound (currently amended) and

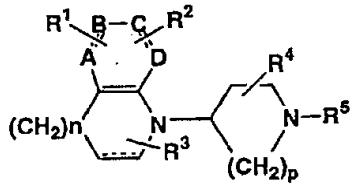
8. ~~An agent~~ comprising an effective amount of the compound of for treating, ameliorating, ~~and preventing~~ spastic paralysis, which ~~contain~~ as the active ingredient ~~the 1,4-substituted cyclic amine derivative as set forth in~~ claim 1 or a pharmacologically acceptable salt thereof.

(currently amended) composition

9. A muscle relaxant which contains as the active ingredient ~~the 1,4-substituted cyclic amine derivative as set forth in~~ an effective amount of the compound of claim 1 ~~or a~~ in a mixture with a pharmacologically acceptable salt thereof.

(currently amended)

10. A process for producing a ~~1,4-substituted cyclic amine derivative represented by the following~~ compound of the formula:

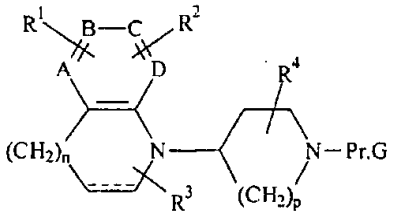


wherein the bond represented by the following formula:

6-12-03

---

and A, B, C, D, R^1, R^2, R^3, R^4, R^5, n, and p are each as defined in claim 1, which comprises removing, if necessary, the protecting group from a 1,4-substituted cyclic amine derivative (IX) represented by the following formula:



(IX)

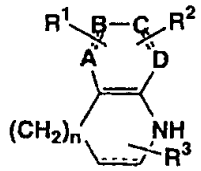
wherein the bond represented by the following formula:

---

and A, B, C, D, R^1, R^2, R^3, R^4, n, and p are each as defined in claim 1; and Pr.G represents hydrogen or a protecting group, and then reacting the same with L-R^5 wherein R^5 is as defined in claim 1; and L represents a leaving group.

(currently amended)

11. A process for producing ~~1,4-substituted cyclic amine derivative (X),~~ a compound of ~~as set forth in~~ claim 1, which comprises reacting a fused cyclic amine represented by the following formula:

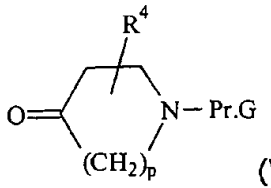


wherein the bond represented by the following formula:

---

and A, B, C, D, R^1, R^2, R^3 and n are each as defined in claim 1 with a cyclic ketone (VIII) represented by the following formula:

OPM 6-12-03



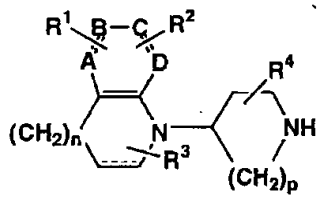
(VIII)

wherein R^4, p, and Pr.G are each as defined in claim 1

in the presence of a reducing agent to thereby give a 1,4-substituted cyclic amine derivative (IX), removing, if necessary, the protecting group therefrom and further reacting the same with L-R^5.

(currently amended)

12. A ~~4-substituted cyclic amine derivative represented by the following~~ compound of the formula:



wherein the bond represented by the following formula:

---

and A, B, C, D, R^1, R^2, R^3, R^4, n, and p are each as defined in claim 1, provided that the case where R^1, R^2, R^3 and R^4 are all hydrogen atoms is excluded.

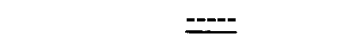
(currently amended)

13. A method for ~~treating a disease to which~~ serotonin ~~antagonism is efficacious,~~ which comprises administering an effective dose of the ~~1,4-substituted cyclic amine derivative as set forth in~~ compound of claim 1, or a pharmacologically acceptable salt thereof, to a person in need of such treatment.

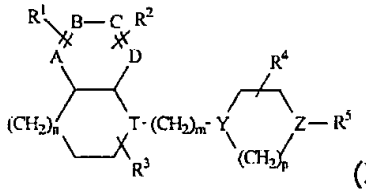
6-17-03

(currently amended) compound of

14. The ~~1,4-substituted cyclic amine derivative as set forth in~~ claim 1, in which the bond represented by the following formula in the formula (I):



is a single bond, represented by the formula (XXI):

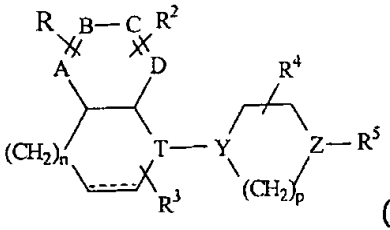


(XXI)

or a pharmacologically acceptable salt thereof.

(currently amended) compound of

15. The ~~1,4 substituted cyclic amine derivative as set forth in~~ claim 1, in which m is 0 in the formula (I), represented by the formula (XXII):



(XXII)

or a pharmacologically acceptable salt thereof.

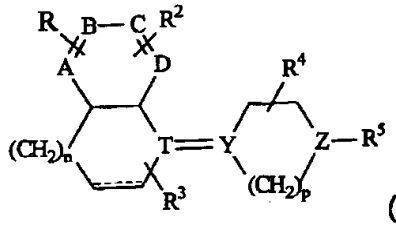
(currently amended) compound of

16. The ~~1,4 substituted cyclic amine derivative as set forth in~~ Claim 1, in which m is 1 to 6 in the formula (I) or a pharmacologically acceptable salt thereof.

6-17-03

(currently amended) compound of

17. A ~~1,4 substituted cyclic amine derivative represented by~~ the formula (XXIII):



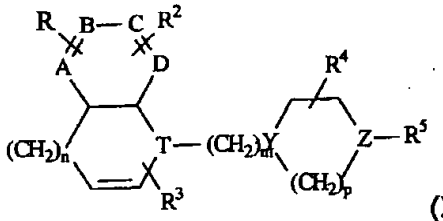
(XXIII)

or a pharmacologically acceptable salt thereof.

(currently amended) compound of

18. The ~~1,4 substituted cyclic amine derivative as set forth in~~ claim 1, in which the bond represented by the following formula in the formula (I):

is a double bond, represented by the formula (XXIV):



(XXIV)

or a pharmacologically acceptable salt thereof.

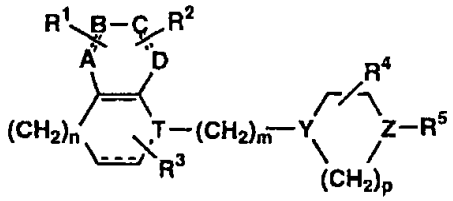
(currently amended) compound of

19. The ~~1,4 substituted cyclic amine derivative as set forth in~~ claim 1, in which the T is nitrogen.

6-12-03

ABSTRACT OF THE DISCLOSURE

A novel ~~1,4-substituted cyclic amine derivative represented by the~~ compound of the ~~following~~ formula:



wherein A, B, C, D, T, Y, and Z represent each methine or nitrogen; R^1, R^2, R^3, R^4, and R^5 represent each a substituent; n represents 0 or an integer of 1 to 3; m represents 0 or an integer of 1 to 6; and p represents an integer of 1 to 3; and pharmacologically acceptable salts thereof. The compound has a serotonin antagonism and is clinically useful as medicament, in particular, for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia.

6-12-03